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(54) **FORMULATIONS SOLIDES, A AU MOINS DEUX PHASES, D'UN ANALGESIQUE OPIOIDE A LIBERATION CONTROLEE**

(54) **SOLID, AT LEAST TWO-PHASE FORMULATIONS OF AN OPIOID ANALGESIC WITH DELAYED RELEASE**

(57) Formulation solide, à au moins deux phases, d'au moins un analgésique opioïde dans une matrice, dans laquelle chacune des deux phases contient au moins un opioïde avec un taux de libération in vitro, selon la méthode de dissolution par un agitateur à ailettes de la Ph. Eur., de plus de 50 % en poids du principe actif après une heure.

(57) A solid, at least two-phase formulation of at least one opioid analgesic in a matrix, where each of the two phases contains at least one opioid with an in vitro release rate by the Ph.Eur. paddle method of more than 50% by weight of active ingredient after one hour.

Solid, at least two-phase formulations of an opioid analgesic with delayed release

Description

The present invention relates to solid, at least two-phase formulations of at least one opioid analgesic, where each of the two phases contains at least one opioid, with an in vitro release rate determined by the Ph.Eur. paddle method of more than 50% by weight after one hour. The invention furthermore relates to a process for producing such formulations.

Opioid drug forms disclosed to date release the active ingredient either with no delay or with classical slowing of release. Such forms with classical slowing of release have either a coating which acts to slow release or contain a homogeneous phase of the active ingredient in an ancillary substance matrix. One-stage release profiles are accordingly achieved. However, the disadvantage of classical slowing of release is that release of the active ingredient starts relatively slowly, which also results in delayed onset of the analgesic effect. Another disadvantage of slowing release by means of a coating is that dose dumping may occur if the coating is damaged by the peristalsis in the digestive tract. This may result in an initial dose so large as to be outside the therapeutic range.

Thus, EP-A 271 193 describes hydromorphone formulations for administration twice a day which contain the active ingredient in a matrix and with which up to 42.5% by weight of the active ingredient are released after one hour. Formulations of this type consist of a homogeneous phase.

EP-A 543 541 describes preparations of the active ingredient flutamide which have a rapid release phase as outer shell and a core which has a release-slowing coating.

It is an object of the present invention to find drug forms which permit both a rapid rise in level of the active ingredient for rapidly diminishing severe pain and a slow release for prolonged pain control.

We have found that this object is achieved by dosage forms which display at least biphasic release of the active ingredient. The solid, at least two-phase drug forms for oral administration, where each phase comprises at least one opioid analgesic, show an in vitro release rate measured by the Ph.Eur. paddle method of

more than 50% of the active ingredient after one hour. Preferred drug forms have a release rate of from 55 up to 80% after one hour, up to 85% after two hours, 60 to 95% after four hours and from 65 to 100% after eight hours. Particularly preferred release rates are from 56 to 70% in the first hour. The drug forms are particularly intended for administration twice a day. Unless otherwise mentioned, the in vitro release rates are determined by the Ph. Eur. paddle method at 100 rpm in 0.1 N HCl at 37°C with UV detection at 270 nm.

Opioid analgesics for the purpose of this invention are:

morphine, codeine, ethylmorphine, dihydrocodeine, hydromorphone, oxycodone, hydrocodone, thebacon, levorphanol, pethidine, ketobemidone, levomethadone, normethadone, fenpipramide, dextromoramide, clofenadol, pentazocine, tilidine, naloxone, piritramide, fentanyl, nefopam, tramadol and buprenorphine or their physiologically tolerated salts.

Preferred opioids are:

codeine, dihydrocodeine, hydrocodone, hydromorphone, morphine, dihydromorphine, oxymorphone, tramadol or mixtures thereof. Very particularly preferred opioids are selected from the group of hydromorphone, morphine, tramadol or their physiologically tolerated salts.

The claimed drug forms comprise therapeutically effective amounts of the opioid active ingredients. In the case of tramadol, 50 - 1000 mg of tramadol hydrochloride are employed per drug form, preferably 100 to 600 mg. This preferably comprises 5 - 50% by weight in the IR phase and 50 - 95% by weight in the SR phase.

In the case of morphine or its physiologically tolerated salts such as morphine sulfate or morphine hydrochloride, 10 mg, 30 mg, 60 mg, 100 mg, 200 mg or 500 mg of active ingredient are employed per drug form, preferably comprising 1 - 20% by weight in the IR phase and 80 - 99% by weight in the SR phase.

In the case of hydromorphone, the drug forms comprise 1 - 150 mg, preferably 2 - 60 mg, in particular 2 - 30 mg, preferably comprising 1 - 15% by weight in the IR phase and 85 - 99% by weight in the SR phase.

The drug forms consist of at least two phases, each phase comprising at least one opioid in a matrix. The opioids can be identical or different. The various phases each display a

different release profile, one phase being rapid release (IR phase; instant release) and intended to achieve a rapid onset of the analgesic effect, while the other phase shows slow release (SR phase, sustained release), in order to achieve an additional prolonged effect.

The control of release can in each case be achieved by the composition of the matrix of the individual phases. This matrix can consist of low molecular weight ancillary substances and/or polymeric binders. The release is not controlled by a release-slowing coating.

Rapid release matrices may, for example, be obtained by the following compositions of ancillary substances:

a) suitable polymeric binders are synthetic or semisynthetic polymers such as water-soluble homo- or copolymers of N-vinylpyrrolidone (NVP) with Fikentscher K values up to 30, with preferred comonomers being vinyl esters, especially vinyl acetate, also hydroxyalkylcelluloses such as hydroxypropylcellulose, alkylcelluloses such as ethylcellulose, as well as polyethylene glycols, preferably those having molecular weights of from 1000 to 20000. Also suitable are methacrylic acid copolymers (Eudragit types) or polyvinyl alcohol. Also suitable as binders are natural polymers such as starch or else starch derivatives such as hydroxyethyl starch, oxidized starches or pregelatinized starches.

b) suitable bulking agents are sugars, for example lactose, glucose or sucrose, sugar alcohols such as maltitol, mannitol, sorbitol, xylitol and isomalt, also degraded starches such as dextrins, especially maltodextrin. Also suitable are microcrystalline cellulose or inorganic salts such as calcium phosphate, dicalcium phosphate or sodium chloride, and, where appropriate, also alkali metal carbonates such as Na_2CO_3.

c) suitable disintegrants are sodium starch glycolate, crosslinked polyvinylpyrrolidone, crosslinked carboxymethylcellulose, bentonites, alginates or croscarmellose.

d) suitable water-soluble wetting agents or water-soluble surfactants are sodium lauryl sulfate, sorbitan fatty acid esters, salts of bile acids and similar pharmaceutically acceptable surface-active substances.

e) further pharmaceutical additives such as colors and/or flavors.

The various components can be employed in the matrix in the following amounts:

a) 0 - 80% by weight
b) 0 - 99% by weight
c) 1 - 8% by weight
d) 0.1 - 10% by weight
e) 0.1 - 5% by weight

The stated amounts are based on the total amount of the ancillary substances (a) to (e), with the amounts of a) and b) being chosen in each case so that the total amount of 100% by weight results.

The slow-release phase may comprise the following ingredients:

Suitable polymeric binders are:

A) soluble homo- and copolymers of NVP with K values from 10 to 100, preferred comonomers being vinyl esters such as vinyl propionate or, in particular, vinyl acetate, also polyvinyl alcohol, polyvinyl acetate, partially hydrolyzed polyvinyl acetate,

B) alkylcelluloses such as methylcellulose or ethylcellulose, hydroxyalkylcelluloses such as hydroxypropylcellulose, hydroxyethylcellulose, and hydroxypropylmethylcellulose, furthermore cellulose esters such as cellulose acetate, cellulose acetate propionate, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate phthalate and uncrosslinked carboxymethylcellulose,

C) methacrylic acid copolymers, with ethyl acrylate being preferred as comonomer, aminoalkyl methacrylate copolymers.

It is also possible to employ mixtures of polymers A), B) and/or C), for example mixtures of 0 - 90% by weight of A), 10 - 70% by weight of B) and 0 - 20% by weight of C).

Each of the phases may furthermore contain additional pharmaceutical ancillary substances such as lubricants, flavor improvers, emulsifiers etc.

The drug forms may also comprise more than two opioid-containing phases when a more pronounced gradation of the slow release is to be achieved. The drug forms may furthermore additionally contain nonopioid-containing phases which may comprise other analgesics such as nonsteroidal antiinflammatory analgesics.

The drug forms according to the invention are preferably in the form of open multilayer tablets in which each phase forms a layer. The drug forms may also be in the form of closed laminated tablets in which the rapid release phase forms the outer coating while the core is formed by one or more slow-release phases. Suitable multiphase drug forms are also inlay tablets (bull-eye tablets) or multiparticulate forms in which individual granules, pellets or other particles which correspond to the slow-release phase are incorporated into a rapid-release phase.

Suitable for producing the drug forms according to the invention are, inter alia, conventional tableting processes, for example processes in which the individual phases in each case are compressed together in the form of granules or pellets. In these cases, the individual phases with their different release characteristics are retained. It is possible in this way to obtain monolayer or multilayer tablets.

The drug forms according to the invention are preferably produced by a melt extrusion process, in which case the active ingredients are mixed with the ancillary substances in the melt and extruded through one or more dies or breaker plates, and then the still thermoplastic materials are subjected to shaping. This process is preferably carried out in the absence of solvents. Particularly suitable for producing open or closed laminated tablets is the coextrusion process in which the compositions intended for the individual phases are melted and extruded separately, after which the still plastic strands, ribbons or layers are brought together and shaped. A coextrusion process of this type is described, for example, in DE 195 39 361. Alternatively, it is also possible to produce multilayer tablets by combining melts in an injection molding process, applying successive layers in the mold, or by 2-component injection molding.

Production preferably takes place in twin-screw extruders with or without kneading disks.

It is furthermore possible to incorporate one of the phases in solid form into the other phase in the form of a melt or a still plastic material. The precondition for this is that the solid phase does not dissolve in the melt, which can be achieved by suitable choice of the ancillary substance, or by one matrix being coated or dusted with powder before incorporation into the other.

Solid, at least two-phase drug forms which can be produced by the process according to the invention are, in particular, tablets, preferably oblong tablets, coated tablets, pastilles or pellets. The drug forms can also be provided with a taste-masking coating.

The opioid drug forms obtained according to the invention display, because they are composed of a rapid-release phase and at least one slow-release phase, release kinetics which are particularly desirable for strong analgesics. Forms of this type can be produced particularly straightforwardly and reliably by the process according to the invention.

Administration of the dosage forms according to the invention achieves not only a rapid onset of the analgesic effect but also a long-lasting pain control. It was surprising that plasma levels in the pain-relevant range could be achieved even after 5 h.

In the case of tramadol, blood plasma levels of 90 - 200 mg/ml, preferably 100 - 180 mg/ml, particularly preferably 110 - 165 mg/ml, are achieved 5 hours after a single administration under fasting conditions.

The compositions mentioned in the following Examples are preferably coextruded in a Werner & Pfleiderer ZSK 30 twin-screw extruder with an output of 2 kg/hour in each case. The shaping of the still plastic extrudate takes place as described in EP-A 240 906 by calendering.

Formulation 1:

Extruder 1:

1 kg of a mixture of 40% by weight of tramadol HCl, 15% by weight of ethylcellulose (Ethocel N100), 35% by weight of isomalt, 7% by weight of polyvinylpyrrolidone K30 and 3% by weight of hydrogenated castor oil (Cutina HR) were mixed in a twin-screw extruder.

Section temperatures: 44, 80, 121, 99, 92, 82 °C
Die: 80 °C

Extruder 2:

1 kg of a mixture of 35% by weight of tramadol HCl, 34% by weight of hydroxypropylmethylcellulose (Methocel K100M) and 31% by weight of hydroxypropylcellulose (Klucel EF) were mixed in a twin-screw extruder.

Section temperatures: 44, 80, 121, 99, 92, 82°C
Die: 80 °C

The drug forms displayed the following in vitro release.

Time in minutes	% by weight of active ingredient released
60	71.9
120	81.9
180	87.9
240	90.9
300	95.6
360	97.0
420	97.5
480	98.0

Example 2:

Extruder 1:

1 kg of a mixture of 40% by weight of tramadol HCl, 15% by weight of ethylcellulose, 35% by weight of isomalt, 7% by weight of polyvinylpyrrolidone K30 and 3% by weight of hydrogenated castor oil were mixed in a twin-screw extruder.

Section temperatures: 44, 80, 121, 99, 92, 82 °C
Die: 80°C

Extruder 2:

1 kg of a mixture of 52% by weight of tramadol HCl, 36% by weight of hydroxypropylmethylcellulose and 12% by weight of hydroxypropylcellulose were mixed in a twin-screw extruder.

Section temperatures: 43, 78, 123, 124, 131, 131 °C
Die: 131°C

The tablets displayed the following in vitro release:

Time in minutes	% by weight of active ingredient
60	58.5
120	70.4
180	81.3
240	88.8
300	93.8
360	96.2
420	97.0
480	97.5

The release rate was measured by the Ph.Eur. paddle method in 0.1 N HCl at 100 rpm und 37 °C with UV detection at 270 nm.

We claim:

1. A solid, at least two-phase formulation of at least one opioid analgesic in a matrix,

where each of the two phases contains at least one opioid with an in vitro release rate by the Ph.Eur. paddle method of more than 50% by weight of active ingredient after one hour.

2. A formulation as claimed in claim 1, having a release rate of 55-80% by weight of active ingredient after one hour, 58 - 85% by weight after two hours, 60-95% by weight after four hours and 65-100% by weight after eight hours.

3. A formulation as claimed in claim 1, comprising a rapid-release phase and a slow-release phase.

4. A formulation as claimed in claim 1, comprising as opioid hydromorphone, morphine, tramadol or their physiologically tolerated salts.

5. A process for producing a formulation as claimed in any of claims 1 to 4, which comprises the ingredients of each of the phases being separately melted in an extruder, coextruded and shaped to drug forms.

Solid, at least two-phase formulations of an opioid analgesic with delayed release

Abstract

A solid, at least two-phase formulation of at least one opioid analgesic in a matrix, where each of the two phases contains at least one opioid with an in vitro release rate by the Ph.Eur. paddle method of more than 50% by weight of active ingredient after one hour.